Exhibit A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SILVERGATE PHARMACEUTICALS, INC., Plaintiff, v. BIONPHARMA INC., Defendant.	C.A. No. 18-1962 (LPS) C.A. No. 19-1067 (LPS)

DEFENDANT BIONPHARMA'S INVALIDITY CONTENTIONS
PURSUANT TO DELAWARE DEFAULT STANDARD RULE 4(d)

Pursuant to Paragraph 4(d) of the District of Delaware Default Standard for Discovery, footnote 3 therein, and the Scheduling Order entered in the above-captioned action on December 4, 2019 (*see* 18-cv- 1962 D.I.[1] 29), and the Court's April 22, 2020 Order, Defendant Bionpharma Inc. ("Bionpharma"), hereby provides Plaintiff Silvergate Pharmaceuticals, Inc. ("Plaintiff" or "Silvergate") its initial invalidity contentions regarding the asserted claims of U.S. Patent Nos. 9,669,008 ("the '008 patent"); 9,808,442 ("the '442 patent"); 10,039,745 ("the '745 patent"); and 10,154,987 ("the '987 patent") (collectively, "patents-in-suit"). Bionpharma has produced or will produce concurrently herewith their document production accompanying these contentions.

I. General Statements.

Bionpharma submits these invalidity contentions based upon information presently available. Discovery is ongoing and the claims have not yet been construed by the Court. Therefore, Bionpharma reserves the right to supplement, alter, amend and/or modify these contentions based on further investigation, fact or expert discovery, evaluation of the scope and

[1] All "D.I." or Docket Item citations henceforth shall be to the 18-cv-1962 docket.

content of the prior art, any claim construction from the Court, or as a result of Plaintiff's asserted claims and contentions.

To the extent that Plaintiff is permitted to assert additional claims not presently identified in its infringement contentions, Bionpharma reserves the right to address the invalidity of such claims. Bionpharma's invalidity positions in these contentions may be in the alternative and do not constitute any concession by Bionpharma for purposes of claim construction or infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000).

Furthermore, these contentions are provided without prejudice to Bionpharma's right to introduce at trial any subsequently-discovered evidence or expert opinions relating to currently-known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Moreover, facts, documents and things now known may be imperfectly understood and, accordingly, such facts, documents and things may not be included in the following contentions. Bionpharma reserves the right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents and things notwithstanding the written statements herein. Bionpharma further reserves their right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents and things that are not currently recalled but might be recalled at some time in the future.

Bionpharma objects to the disclosure of information that is protected by the attorney-client privilege, the attorney work-product immunity, the common interest privilege or any other applicable privilege or immunity. To the extent that Bionpharma inadvertently discloses information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege or any other applicable privilege

or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The information set forth below is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other action, on the grounds of privilege, relevance, materiality or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement or clarify any of the statements provided below at any time. Bionpharma further reserves the right to amend and/or supplement these contentions in accordance with the Federal Rules of Civil Procedure and the Rules of this Court.

Bionpharma reserves the right to allege the invalidity of the asserted claims on bases other than those disclosed herein.

A. Asserted Claims.

On March 5, 2020, Plaintiff provided Bionpharma with its Initial Claim Charts pursuant to Paragraph 4(c) of the Delaware Default Standard. In these Initial Claim Charts, Plaintiff asserted that the products described in Bionpharma's ANDA infringe claims 1-10 of the '008 patent, claims 16, 18-24, and 26-30 of the '442 patent, claims 1, 3-11, and 13-20 of the '745 patent, and claims 18, 20-25, and 27-30 of the '987 patent (the "Asserted Claims"). In view of Plaintiff's Initial Claim Charts, the following invalidity contentions address the Asserted Claims.

B. Claim Construction.

The Court has not construed the Asserted Claims. Bionpharma's position on the invalidity of particular claims will depend on what positions Plaintiff takes on claim construction, and whether and how these claims are construed by the Court. Bionpharma therefore reserves the right to identify additional prior art or to supplement their disclosures or contentions in light of any construction by the Court of the Asserted Claims of the patents-in-

suit. The Invalidity Contentions that Bionpharma presents herein are based, at least in part, on Bionpharma's current understanding of the Asserted Claims and on Bionpharma's current understanding of Plaintiff's positions on claim construction.

To the extent that these Invalidity Contentions reflect constructions of claim terms that may be consistent with or implicit in the Plaintiff's Initial Claim Charts, no inference is intended, nor should any inference be drawn, that Bionpharma agrees with such claim constructions. Bionpharma takes no position on any matter of claim construction in these Initial Invalidity Contentions. Any statement herein describing or tending to describe any claim element is provided solely for the purpose of understanding the relevant prior art or other basis for invalidity. Bionpharma expressly reserves the right to propose any claim construction they consider appropriate and/or contest any claim construction they consider inappropriate.

In part because of the uncertainty of claim construction, these Invalidity Contentions may be made in the alternative and are not necessarily intended to be consistent with each other, and should be viewed accordingly. Furthermore, Bionpharma's inclusion of prior art that would render a claim anticipated or obvious based on a particular scope or construction of the claim, including that apparently applied by the Plaintiff in their Initial Claim Charts, is not, and should in no way be seen as, an adoption or admission as to the accuracy of such scope or construction. Bionpharma reserves all rights to further supplement or modify the positions and information in these Invalidity Contentions, including without limitation, the prior art and grounds of invalidity set forth herein, after the Court has construed the asserted claims of the patents-in-suit.

C. Ongoing Discovery and Disclosures.

Discovery in this case and Bionpharma's investigation, including Bionpharma's search for prior art, is ongoing. Bionpharma therefore reserves the right to further supplement or alter the positions taken and information disclosed in these Invalidity Contentions including, without

limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. To date, Plaintiff has not yet produced any documents concerning its own prior art Epaned™ Kit (Epaned Powder for Oral Solution) product; thus, Bionpharma expressly reserves the right to amend these Initial Invalidity Contentions to propound additional contentions based on documents Plaintiff produces concerning at least its Epaned™ Kit product.

Moreover, because expert discovery has not started, Bionpharma reserves the right to amend these Invalidity Contentions as a result of new information disclosed through the parties' experts. Therefore, Bionpharma reserves all rights to further supplement or amend these Invalidity Contentions if and when further information becomes available.

D. Prior Art Identification and Citation.

It should be recognized that a person of ordinary skill in the art would generally read a prior art reference as a whole and in the context of other publications, literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior art reference, a person of ordinary skill in the art would rely upon other information including other publications and general scientific or engineering knowledge. Bionpharma therefore reserves the right to rely upon other unidentified portions of the prior art references and on other publications and expert testimony to provide context and to aid understanding and interpretation of any identified portions. Bionpharma also reserves the right to rely upon other portions of the prior art references, other publications, and the testimony of experts to establish that the alleged inventions were inherently disclosed in the prior art and/or would have been obvious to a person of ordinary skill in the art, including on the basis of modifying or combining certain cited references. Bionpharma also reserve the right to rely upon any admissions relating to prior art in the patents-in-suit or their respective prosecution histories.

In addition, Bionpharma reserves the right to rely on all prior art produced or to be produced by Plaintiff. To date, Plaintiff has not yet produced any documents concerning its own prior art Epaned™ Kit (Epaned Powder for Oral Solution) product; thus, Bionpharma expressly reserves the right to amend these Initial Invalidity Contentions to propound additional contentions based on documents Plaintiff produces concerning at least its Epaned™ Kit product.

E. Reservation of Rights.

Bionpharma reserves all rights to further supplement or modify these Invalidity Contentions, including the prior art disclosed and the stated grounds of invalidity. In addition, Bionpharma reserves the right to prove the invalidity of the Asserted Claims on bases other than those disclosed in these disclosures and contentions and/or amend these contentions at a later date.

II. The Patents-in-Suit.

A. The '008 Patent.

The '008 patent, entitled "ENALAPRIL FORMULATIONS," issued from United States Patent Application No 15/081,603 ("'603 application"), which was filed on or about March 25, 2016, and claims priority to United States Provisional Application No. 62/310,198 ("'198 application"), filed on or about March 18, 2016. The '008 patent lists Gerold L. Mosher and David W. Miles as inventors, and Silvergate is listed as the assignee on the face of the patent. The patent issued with 20 claims. '008 patent at cover.

The asserted claims from the '008 patent are as follows:

> 1. A stable oral liquid formulation, comprising: (i) about 1 mg/ml enalapril maleate; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iii) about 1 mg/ml of a preservative that is sodium benzoate; and (iv) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3º C. for at least 12 months; wherein the stable oral liquid formulation has about 95% or greater of the

initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

2. The formulation of claim 1, further comprising a flavoring agent.

3. The formulation of claim 1, wherein the pH is between about 3 and about 3.5.

4. The formulation of claim 3, wherein the pH is about 3.3.

5. The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

6. The formulation of claim 5, wherein the citrate concentration in the buffer is about 10 mM.

7. The formulation of claim 1, wherein the formulation is stable at about 5±3º C. for at least 18 months.

8. The formulation of claim 1, wherein the formulation is stable at about 5±3º C. for at least 24 months.

9. The formulation of claim 1, wherein the formulation does not contain mannitol.

10. The formulation of claim 1, wherein the formulation does not contain silicon dioxide.

B. The ’442 Patent.

The ’442 patent, also entitled “ENALAPRIL FORMULATIONS,” issued from United States Patent Application No 15/613,622 (“’622 application”), which was filed on or about June 5, 2017, and purports to be a continuation of the ’603 application, and claims its earliest priority to the ’198 application. The ’442 patent lists Gerold L. Mosher and David W. Miles as inventors, and Silvergate is listed as the assignee on the face of the patent. The patent issued with 30 claims. ’442 patent at cover.

The asserted claims form the ’442 patent are as follows:

16. A method of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising: (i) about 1 mg/ml enalapril maleate; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and (iii) about 1 mg/ml of a preservative that is sodium benzoate; and (iv) water; wherein the pH of the stable oral liquid formulation is less than about 3.5; wherein the

stable oral liquid formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

18. The method of claim 16, wherein the pH is between about 3 and about 3.5.

19. The method of claim 16, wherein the pH is between about 3.3.

20. The method of claim 16, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

21. The method of claim 16, wherein the stable oral liquid formulation is stable at about 5±3º C. for at least 24 months.

22. The method of claim 16, wherein the stable oral liquid formulation does not contain mannitol or silicon dioxide.

23. The method of claim 16, wherein the heart failure is congestive heart failure.

24. A method of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising: (i) about 1 mg/ml enalapril maleate; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and (iii) about 1 mg/ml of a preservative that is sodium benzoate; and (iv) water; wherein the pH of the stable oral liquid formulation is less than about 3.5; wherein the stable oral liquid formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

26. The method of claim 24, wherein the pH is between about 3 and about 3.5.

27. The method of claim 24, wherein the pH is between about 3.3.

28. The method of claim 24, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

29. The method of claim 24, wherein the stable oral liquid formulation is stable at about 5±3º C. for at least 24 months.

30. The method of claim 24, wherein the stable oral liquid formulation does not contain mannitol or silicon dioxide.

C. The ’745 Patent.

The ’745 patent, also entitled “ENALAPRIL FORMULATIONS,” United States Patent Application No 15/802,341 (“’341 application”), which was filed on or about November 2, 2017, and which purports to be a continuation of the ’622 application. The ’745 patent claims further priority to the ’603 and ’198 applications. The ’745 patent lists Gerold L. Mosher and David W. Miles as inventors, and Silvergate is listed as the assignee on the face of the patent. The patent issued with 20 claims. ’745 patent at cover.

The asserted claims of the ’745 patent are as follows:

> 1. A stable oral liquid formulation, comprising: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; (iii) about 0.7 to about 1.2 mg/ml sodium benzoate; and (iv) water; wherein the formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
>
> 3. The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
>
> 4. The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
>
> 5. The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
>
> 6. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.
>
> 7. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
>
> 8. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.
>
> 9. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about 5±3º C. for at least 18 months.
>
> 10. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about 5±3º C. for at least 24 months.

> 11. A stable oral liquid formulation, comprising: (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate; (iii) about 3% to about 25% (w/w of solids) sodium benzoate; and (iv) water; wherein the formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
>
> 13. The stable oral liquid formulation of claim 11 further comprising a flavoring agent.
>
> 14. The stable oral liquid formulation of claim 11, wherein the formulation does not contain mannitol.
>
> 15. The stable oral liquid formulation of claim 11, wherein the formulation does not contain silicon dioxide.
>
> 16. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is less than about 3.5.
>
> 17. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.
>
> 18. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is about 3.3.
>
> 19. The stable oral liquid formulation of claim 11, wherein the formulation is stable at about 5±3º C. for at least 18 months.
>
> 20. The stable oral liquid formulation of claim 11, wherein the formulation is stable at about 5±3º C. for at least 24 months.

D. The ’987 Patent.

The ’987 patent, also entitled “ENALAPRIL FORMULATIONS,” United States Patent Application No 16/003,994 (“’994 application”), which was filed on or about June 8, 2018, and which purports to be a continuation of the ’341 application. The ’987 patent claims further priority to the ’622, ’603, and ’198 applications. The ’987 patent lists Gerold L. Mosher and David W. Miles as inventors, and Silvergate is listed as the assignee on the face of the patent. The patent issued with 30 claims. ’987 patent at cover.

The asserted claims of the '987 patent are as follows:

18. A method of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation, the stable oral liquid formulation comprising: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; (iii) about 0.7 to about 1.2 mg/ml sodium benzoate; and (iv) water; wherein the formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

20. The method of claim 18, wherein the formulation does not contain mannitol or silicon dioxide.

21. The method of claim 18, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

22. The method of claim 18, wherein the pH of the stable oral liquid formulation is about 3.3.

23. The method of claim 18, wherein the formulation is stable at about 5±3º C. for at least 24 months.

24. The method of claim 18, wherein the heart failure is congestive heart failure.

25. A method of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation, the stable oral liquid formulation comprising: (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; (iii) about 0.7 to about 1.2 mg/ml sodium benzoate; and (iv) water; wherein the formulation is stable at about 5±3º C. for at least 12 months; and wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

27. The method of claim 25, wherein the formulation does not contain mannitol or silicon dioxide.

28. The method of claim 25, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

29. The method of claim 25, wherein the pH of the stable oral liquid formulation is about 3.3.

30. The method of claim 25, wherein the formulation is stable at about 5±3º C. for at least 24 months.

III. Invalidity Contentions.

A. Prior Art Invalidity (35 U.S.C. §§ 102, 103).

1. *Identification of Prior Art.*

Bionpharma contends that the references[2] identified in this section below are prior art to the patents-in suit:

Patent Literature

Abbreviation	Patent/Publication No.	Issue/Publication Date
'747 Patent[3]	U.S. Patent No. 8,568,747 B1	October 29, 2013
'366 Patent	U.S. Patent No. 8,778,366 B2	July 15, 2014
'214 Patent	U.S. Patent No. 9,855,214 B2	January 2, 2018
'553 Patent	U.S. Patent No. 9,968553 B1	May 15, 2019

Non-Patent Literature

Abbreviation	Publication	Publication Date
Schlatter	J. Schlatter et al., *Stability of Enalapril Solutions Prepared from Tablets in Sterile Water*, 27 AUSTRALIAN J. HOSPITAL PHARMACY 395	1997
Nahata	M. Nahata et al., *Stability of Enalapril Maleate in Three Extemporaneously Prepared Oral Liquids*, 55 AM. J. HEATH-SYST. PHARM. 1155	June 1, 1998

[2] Pursuant to Delaware Default Standard for Discovery Rule 4(d), copies of the patent and non-patent literature references are being produced to Plaintiff's counsel concurrently herewith.
[3] The '747, '366, '214, and '553 patents are collectively referred to as the "Epaned Kit Patents."

Abbreviation	Publication	Publication Date
Helin-Tanninen	Helin-Tanninen, M. et al., *Comparison of six different suspension vehicles in compounding of oral extemporaneous nifedipine suspension for paediatric patients*, 19 EURO. J. HOSPITAL PHARM. 432 (2012)	2012
Epaned Kit PI	Epaned™ (enalapril) for Oral Solution Prescribing Information (Revised 09/2014)	September 2014

Sales/Offers for Sale

Abbreviation	Publication	Sale/Offer for Sale Date
Epaned Kit	Epaned™ Kit (enalapril) for Oral Solution	August 2013

The elements of the asserted claims are located in the aforementioned prior art, as identified in Sections III.A.2-5, below. A person of ordinary skill in the art ("POSA") in the relevant time period would have understood and interpreted the cited passages in the context of the prior art references as a whole, as well as in the context of the state of the art. Bionpharma expressly reserves the right to rely on the entirety of the references identified, including passages not particularly referred to. Bionpharma also expressly reserves the right to rely on other publications and expert testimony as aids in understanding and interpreting the cited references and passages, as providing context thereof, and as additional evidence that the prior art discloses a claim element. Bionpharma also reserves the right to rely on documents Plaintiff produces in discovery, particularly pertaining to its Epaned Kit product. With respect to the Epaned Kit, Bionpharma intends to rely on documents to be produced by Plaintiff identifying the qualitative and quantitative formulation of the Epaned Kit, its chemical and physical properties, including stability, and evidencing offers for sale and sales.

Unless otherwise stated, it should be presumed that Bionpharma intends to rely upon each piece of prior art in its entirety, including references cited in and/or referenced within the above references. Bionpharma may also rely on art cited during the prosecution of the patents-in-suit and related patent applications.

Bionpharma also reserves the right to establish what was known to a POSA through other prior art. Moreover, Bionpharma further reserves the right to rely on not presently-cited portions of the prior art references, other prior art or prior art references, and relevant testimony to establish that a POSA would have been motivated to combine, with a reasonable expectation of success, certain of the identified prior art to render obvious the Asserted Claims. Finally, Bionpharma reserves the right to rely on any additional prior art cited during prosecution of the applications leading to the patents-in-suit which are not explicitly listed above.

The '747 and '366 patents, the Epaned Kit PI, and the Epaned Kit qualify as prior art under 35 U.S.C. § 102(b), while the '214 and '553 patents qualify as prior art under at least 35 U.S.C. § 102(e).

2. *Anticipation/Obviousness of the '008 Patent Asserted Claims.*

a. The Asserted Claims of the '008 patent Are Anticipated/Obvious over the Epaned Kit Patents.

The Epaned Kit Patents all share a common specification and disclose oral liquid formulations of enalapril maleate that comprise 1 mg/mL of enalapril maleate, a buffering agent such as sodium citrate, and a preservative that can be citric acid, a paraben or mixture of parabens, and/or benzoic acid. *See, e.g.*, '747 patent 3:12-49, 6:23-47, 7:17-41, 7:51-59, 22:55-23:40. By March 18, 2015, the POSA reading the buffer and preservative portions of the specifications of the Epaned Kit Patents would understand that citric acid could also serve as a buffer in combination with sodium citrate, and that that an oral liquid formulation of enalapril

maleate could be prepared by using the sodium salt of benzoic acid as a preservative, and that methylparaben and propylparaben could also be used together as a preservative.

Moreover, while the Epaned Kit Patents teach that the disclosed enalapril maleate oral liquid formulations may contain other excipients, such as mannitol, lactose, sucrose, or colloidal silicon dioxide, such liquid formulations would still fall within the broad scope of the broader asserted claims of the '008 patent (claims 1-8), which recite genuses of enalapril maleate oral liquid formulations that comprise a specific buffer combination (citric acid and sodium citrate) and a specific preservative (sodium benzoate), in specific amounts, and water, and that may include other ingredients. Thus, that the enalapril maleate liquid formulations disclosed in the Epaned Kit Patents may include other excipients, such as mannitol and colloidal silicon dioxide, is irrelevant to the invalidity of claims 1-8 of the '008 patent, because such formulations are included within the broad scope of those claims.

In short, the shear breadth of claims 1-8 of the '008 patent cover numerous enalapril liquid formulations disclosed in the Epaned Kit Patents, including those specifically with citric acid and sodium citrate as a buffer combination, and with sodium benzoate as a preservative. Although the asserted claims of the '008 patent by their plain language require specific amounts of the recited buffer combination and preservative, Plaintiff—through its infringement contentions in the instant action—has taken the position that buffers qualitatively and quantitatively beyond the "about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate," and preservatives qualitatively and quantitatively beyond the "about 1 mg/ml . . . sodium benzoate," recited in the asserted '008 patent claims are equivalent to the claimed buffer combination and preservative, and therefore infringe the asserted claims under the doctrine of equivalents. Of course, such a broad application of the doctrine of equivalents ensnares the

numerous prior art enalapril liquid formulations disclosed in the Epaned Kit Patents. Nevertheless, the Epaned Kit Patents disclose enalapril liquid formulations that include sodium citrate as a buffer ('747 patent 7:26-27), and the POSA would immediately recognize that the acid form of sodium citrate (citric acid) could also be used in combination with the salt form as a buffer combination suitable for use in the disclosed enalapril liquid formulations (the Epaned Kit Patents also teach that citric acid may be used in the disclosed enalapril liquid formulations as a preservative, *id*. at 7:51-5351). Similarly, the POSA reading the common specification would immediately recognize that the sodium salt of benzoic acid can be used as a suitable buffer in the disclosed enalapril liquid formulations, from the express teaching therein that benzoic acid was a suitable buffer (*id*. at 7:51-57).

With respect to the buffer concentration limitations, Plaintiff has essentially ignored those limitations in connection with its infringement contentions. Nevertheless, through routine optimization, the POSA preparing the 1 mg/mL enalapril maleate liquids disclosed in the Epaned Kit Patents would have used sodium citrate in a concentration of about 5-10 mM, rendering obvious the limitations of asserted claims 5 and 6 of the '008 patent. The POSA would also know that the 1 mg/mL enalapril maleate liquids disclosed in the Epaned Kit Patents are sometimes prepared by reconstitution with Ora-Sweet SF, which contains sodium citrate in the concentrations required in asserted '008 patent claims 5 and 6, as discovery will show. '747 patent 8:35-37, 27:30-28:29. At the very least, it would have required nothing more than routine experimentation to arrive at the claimed concentrations recited in asserted claims 5 and 6, rendering them obvious.

Next, the Epaned Kit Patents teach that the disclosed enalapril liquid formulations may be stable (defined as having at least 90% enalapril and 5% or less total impurities or substances at

the end of a given storage period) for at least 36 weeks (or at least 9 months) in refrigerated conditions (5±3 C.). *Id*. at 13:5-33. This teaching renders the "at least 12 months"-stability limitations of the asserted '008 patent claims obvious. Moreover, through testing and optimization, the POSA would have been able to modify the enalapril liquid formulations disclosed in the Epaned Kit Patents to be stable at refrigerated conditions for at least 18 months and 24 months, as required by '008 patent asserted claims 7 and 8. With respect to the pH limitations, the POSA would know that pH changes in unbuffered enalapril formulations could affect stability. *See, e.g.*., Schlatter at 397. The POSA would also know that the Epaned Kit Patents taught that the enalapril liquid formulations prepared therein could be prepared from powders by reconstitution with Ora-Sweet SF, which the POSA would know was a vehicle buffered with citric acid and sodium citrate and had a pH of approximately 4.2. '747 patent 8:35-37, 27:30-28:29; Helin-Tanninen at 433 (Table 1); *see also*, Epaned Kit PI § 11. From these disclosures, it would have been obvious and within the grasp of the POSA to create an enalapril liquid formulation according to the Epaned Kit patents with a slightly lower pH of 3.3-3.5, rendering the pH limitations of the asserted '008 patent claims (*e.g*. claims 1, 3-4) obvious. The 1 mg/mL enalapril maleate liquid formulations disclosed in the Epaned Kit Patents also may contain a flavoring agent (*see, e.g.*, '747 patent 3:35-39), rendering obvious asserted claim 2 of the '008 patent.

With respect to asserted claims 9 and 10 of the '008 patent, it would have been obvious to omit colloidal silicon dioxide from the enalapril liquid compositions taught in the Epaned Kit Patents, as the POSA would know that colloidal silicon dioxide is insoluble and could result in a clowdy liquid or suspension. The POSA would also have known that mannitol could be omitted from the enalapril liquid formulations disclosed in the Epaned Kit Patents, as at least two

examples in the common specification of the Epaned Kit Patents describe formulations without mannitol, and mannitol is not a required excipient in the disclosed liquid formulations. *See, e.g.*, '747 patent 21:20-23:40 (Examples 1 and 2). Moreover, the POSA would know that mannitol and colloidal silicon dioxide are binder and glidant, respectively, and that those two excipients are unnecessary to a liquid formulation. Therefore, asserted claims 9 and 10 of the '008 patent are anticipated and/or obvious.

Finally, the asserted '008 patent claims recite enalapril liquid formulations with excipients disclosed in the Epaned Kit Patents, and with stability limitations that fall within the stability ranges disclosed in the Epaned Kit Patents. More specifically, the asserted '008 patent claims essentially cover subgenuses of the enalapril liquid formulations disclosed in the Epaned Kit patents. The Epaned Kit Patents disclose 1 mg/mL enalapril maleate liquid formulations with a range of buffers and preservatives that include the buffer combination and preservative recited in the asserted '008 patent claims, and disclose that the enalapril liquid formulations taught therein are stable for at least 9 months, if not longer. Because the asserted claims of the '008 patent recite limitations that fall within prior art ranges, the asserted claims are presumed obvious, and the burden is on Plaintiff to show: (1) that the prior art taught away from the asserted claims of the '008 patent; (2) unexpected results; or (3) secondary considerations. *Galderma Labs., LP. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

For at least these reasons, asserted claims 1-10 of the '008 patent are anticipated and/or obvious based on the Epaned Kit Patents.

b. The Asserted Claims of the '008 patent Are Anticipated/Obvious over the Epaned Kit PI.

The Epaned Kit PI discloses an enalapril maleate powder that is reconstituted with Ora-Sweet SF into a 1 mg/mL enalapril maleate liquid that contains citric acid and sodium citrate as a

buffer, and that further contains methylparaben, propylparaben, and potassium sorbate as preservatives (and contains water). Epaned Kit PI § 11. Moreover, the Ora-Sweet SF is itself a flavoring agent (as it contains sodium saccharin), as explained in both the '747 and '008 patents, rendering obvious the limitation of asserted claim 2. *Id.*; '747 patent 8:13-37; '008 patent 9:33-54. Plaintiff contends that methylparaben and propylparaben are equivalent to the sodium benzoate preservative limitation of the asserted claims of the '008 patent; moreover, it would have been obvious to substitute out the methylparaben/propylparaben combination used in Ora-Sweet SF for the sodium benzoate expressly recited in the asserted claims of the '008 patent.

With respect to the buffer concentration limitations, Plaintiff has essentially ignored those limitations in connection with its infringement contentions. Nevertheless, the 1 mg/mL enalapril maleate liquids disclosed in the Epaned Kit PI are prepared with Ora-Sweet SF, which contains sodium citrate in the concentrations required in asserted '008 patent claims 5 and 6, as discovery will show. At the very least, it would have required nothing more than routine experimentation to arrive at the claimed concentrations recited in asserted claims 5 and 6, rendering them obvious.

As explained above, the POSA would know that upon reconstitution with Ora-Sweet SF, the resulting 1 mg/mL enalapril liquid would have a pH of approximately 4.2 (Helin-Tanninen at 433 (Table 1)), and would also know from the Epaned Kit Patents that such a liquid could be stable for at least 9 months, rendering the stability limitations of asserted claims 1-8 of the '008 patent obvious (it would have been within the POSA's grasp to optimize the reconstituted 1 mg/mL enalapril maleate oral liquid disclosed in the Epaned Kit PI to be stable for at least 2 years in refrigerated conditions).

With respect to asserted claims 9 and 10, as explained above, it would have been obvious to omit colloidal silicon dioxide from the enalapril liquid composition taught in the Epaned Kit

PI, as the POSA would know that colloidal silicon dioxide is insoluble and could result in a cloudy liquid or suspension. The POSA would also know that mannitol and colloidal silicon dioxide are binder and glidant, respectively, and that those two excipients are unnecessary to a liquid formulation. As such, asserted claims 9 and 10 of the '008 patent are anticipated and/or obvious over the Epaned Kit PI.

c. The Asserted Claims of the '008 patent Are Anticipated/Obvious over the Epaned Kit.

Upon information and belief, Plaintiff has offered for sale, and sold the Epaned Kit in the United States since at the latest August of 2013. Based on at least what is set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent in view of the Epaned Kit PI, the offer for sale and/or sale of the Epaned Kit anticipates and/or renders obvious the asserted claims. Moreover, Bionpharma has reason to believe that further discovery in the case from Plaintiff, including discovery on the precise composition of the Epaned Kit (including upon reconstitution), and on stability of the reconstituted liquid, will further support Bionpharma's anticipation/obviousness defense based on Plaintiff's offers for sale and sale of the Epaned Kit. Thus, Bionpharma expressly reserves the right to supplement its contentions based on additional discovery that Bionpharma is currently seeking from Plaintiff regarding its prior art Epaned Kit.

3. *Anticipation/Obviousness of the '442 Patent Asserted Claims.*

a. The Asserted Claims of the '442 patent Are Anticipated/Obvious over the Epaned Kit Patents.

The asserted claims of the '442 patent essentially cover methods of treating heart failure and left ventricular dysfunction by administering to a subject the enalapril maleate oral liquid compositions claimed in the '008 patent. The Epaned Kit Patents expressly disclose using the 1

mg/mL enalapril maleate oral liquid compositions disclosed therein for exactly these purposes. *See, e.g.*, '747 patent at Abstract. For these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit Patents, the asserted claims of the '442 patents are also anticipated and/or obvious based on the Epaned Kit Patents.

b. The Asserted Claims of the '442 patent Are Anticipated/Obvious over the Epaned Kit PI.

The Epaned Kit PI expressly disclose that the 1 mg/mL enalapril maleate oral liquid composition disclosed was indicated for treatment of symptomatic heart failure (including congested heart failure) and asymptomatic left ventricular dysfunction. *See, e.g.*, Epaned Kit PI at §§ 1, 14. For these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit PI, the asserted claims of the '442 patents are also anticipated and/or obvious based on the Epaned Kit PI.

c. The Asserted Claims of the '442 patent Are Anticipated/Obvious over the Epaned Kit.

By March of 2015, the POSA would know that the Epaned Kit Plaintiff was offering for sale and selling was indicated for treatment of symptomatic heart failure (including congested heart failure) and asymptomatic left ventricular dysfunction. *See, e.g.*, Epaned Kit PI at §§ 1, 14. For these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit, the asserted claims of the '442 patents are also anticipated and/or obvious based on the Epaned Kit.

4. *Anticipation/Obviousness of the '745 Patent Asserted Claims.*

a. The Asserted Claims of the '745 patent Are Anticipated/Obvious over the Epaned Kit Patents.

Asserted claims 1 and 3-10 of the '745 patent are essentially the same as asserted claims 1-10 of the '008 patent, except that asserted claims 1 and 3-10 of the '745 patent recite ranges for the required amounts of enalapril, buffer combination, and preservative (the asserted '745 patent claims also broaden enalapril to cover its pharmaceutically acceptable salts, and independent claim 1 does not include a pH limitation (although that is covered by dependent claim 6)). Thus, asserted claims 1 and 3-10 of the '745 patent are essentially broader versions of asserted claims 1-10 of the '008 patent.

Meanwhile, asserted claims 11 and 13-20 of the '745 patent claim the enalapril oral liquid formulations by specifying weight percentages of solids for the required enalapril, buffer combination, and preservative. The required weight percentage of enalapril ("about 10% to about 25%") is disclosed in the Epaned Kit Patents. *See, e.g.*, '747 6:41-47. As explained above in connection with the asserted claims of the '008 patent, the Epaned Kit Patents teach that the enalapril maleate liquids disclosed therein can contain sodium citrate as a buffer and benzoic acid (or sodium benzoate) as a preservative, and expressly disclose preparation of the liquids disclosed therein with Ora-Sweet SF, which contains citric acid and sodium citrate, and methylparaben/propylparaben as a preservative. Through additional testing and optimization, the POSA would have inevitably arrived at the claimed weight percentages for required citric acid/sodium citrate buffer and sodium benzoate preservative, as required in asserted claims 11 and 13-20 of the '745 patent.

For these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit Patents, asserted claims 1 and 3-

11 and 13-20 of the '745 patent are also anticipated and/or obvious based on the Epaned Kit Patents.

b. Asserted claims 1 and 3-10 of the '745 patent Are Anticipated/Obvious over the Epaned Kit PI.

As explained above, asserted claims 1 and 3-10 of the '745 patent are essentially broader versions of asserted claims 1-10 of the '008 patent. Thus, for the reasons set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit PI, asserted claims 1 and 3-10 of the '745 patent are also anticipated and/or obvious based on the Epaned Kit PI.

c. The Asserted Claims of the '745 patent Are Anticipated/Obvious over the Epaned Kit.

As explained above, asserted claims 1 and 3-10 of the '745 patent are essentially the same as asserted claims 1-10 of the '008 patent, except that asserted claims 1 and 3-10 of the '745 patent recite ranges for the required amounts of enalapril, buffer combination, and preservative (the asserted '745 patent claims also broaden enalapril to cover its pharmaceutically acceptable salts, and independent claim 1 does not include a pH limitation (although that is covered by dependent claim 6)). Thus, asserted claims 1 and 3-10 of the '745 patent are essentially broader versions of asserted claims 1-10 of the '008 patent.

Meanwhile, asserted claims 11 and 13-20 of the '745 patent claim the enalapril oral liquid formulations by specifying weight percentages of solids for the required enalapril, buffer combination, and preservative. Upon information and belief, additional discovery from Plaintiff will show that the reconstituted liquid formulation of the Epaned Kit includes enalapril, citric acid, and sodium citrate in the weight percentages required by asserted claims 11 and 13-20 of the '745 patent. Furthermore, it would have been obvious to a POSA as of March of 2015 to substitute sodium benzoate for the methylparaben/propylparaben preservative used in the

reconstituted Epaned Kit liquid, and it would have required nothing more than routine experimentation to arrive at the required weight percentage of sodium benzoate.

For these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 patent based on the Epaned Kit, asserted claims 1 and 3-11 and 13-20 of the '745 patent are also anticipated and/or obvious based on the Epaned Kit.

5. *Anticipation/Obviousness of the '987 Patent Asserted Claims*.

a. The Asserted Claims of the '987 patent Are Anticipated/Obvious over the Epaned Kit Patents.

Asserted claims 18, 20-25, and 27-30 cover methods of treating heart failure and left ventricular dysfunction by essentially administering the enalapril liquids recited in asserted claims 1 and 3-10 of the '745 patent, which, as explained above, are merely broader versions of asserted claims 1-10 of the '008 patent. Thus, for these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 and '442 patents based on the Epaned Kit Patents, asserted claims 18, 20-25, and 27-30 of the '987 patent are also anticipated and/or obvious based on the Epaned Kit Patents.

b. The Asserted Claims of the '987 patent Are Anticipated/Obvious over the Epaned Kit PI.

Asserted claims 18, 20-25, and 27-30 cover methods of treating heart failure and left ventricular dysfunction by essentially administering the enalapril liquids recited in asserted claims 1 and 3-10 of the '745 patent, which, as explained above, are merely broader versions of asserted claims 1-10 of the '008 patent. Thus, for these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 and '442 patents based on the Epaned Kit PI, asserted claims 18, 20-25, and 27-30 of the '987 patent are also anticipated and/or obvious based on the Epaned Kit PI.

c. The Asserted Claims of the '987 patent Are Anticipated/Obvious over the Epaned Kit.

Asserted claims 18, 20-25, and 27-30 cover methods of treating heart failure and left ventricular dysfunction by essentially administering the enalapril liquids recited in asserted claims 1 and 3-10 of the '745 patent, which, as explained above, are merely broader versions of asserted claims 1-10 of the '008 patent. Thus, for these reasons, and those set forth above with respect to anticipation/obviousness of the asserted claims of the '008 and '442 patents based on the Epaned Kit, asserted claims 18, 20-25, and 27-30 of the '987 patent are also anticipated and/or obvious based on the Epaned Kit.

6. *Secondary Considerations of Nonobviousness*.

In its First Supplemental Response to Defendants' First Set of Joint Interrogatories (Nos. 1-2), Plaintiff has alleged the following secondary considerations of nonobviousness: commercial success, industry praise, long-felt but unsolved needs, "recognition of a problem," failure of others, "unexpected properties," and copying. However, Plaintiff has come forward with absolutely no facts supporting its allegations. Plaintiff of course bears the burden of coming forward with secondary considerations of nonobviousness and facts supporting them, but has failed to do so. Bionpharma reserves the right to supplement these initial contentions after Plaintiff meets its burden of production on this issue.

Moreover, while one of the named inventors, Gerald L. Mosher, Ph.D., submitted a declaration during prosecution of at least the '603 application allegedly showing that the claimed formulations exhibited unexpected stability versus the oral liquid formulations disclosed in the Epaned Kit Patents ('603 Appl., Feb. 3, 2017 Decl. of Gerold Mosher under 37 C.F.R. § 1.132 ("Mosher Decl.) ¶¶ 14-23), the Mosher declaration is misleading and inaccurate and therefore

does not show unexpected results, as it did not provide any stability data on the Epaned Kit Patents enalapril liquids under refrigerated conditions.

B. Invalidity under 35 U.S.C. § 112

1. *The Asserted Claims of the '008 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Written Description.*

The Asserted Claims of the '008 patent claims are invalid under 35 U.S.C. § 112(a), for insufficient written description at least because the specification of the '008 patent does not "reasonably convey[] to those skilled in the art that the inventor[s] had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '008 patent does not convey to a person of skill in the art that the alleged inventors were in possession of the genuses of oral liquid formulations claimed.

The asserted claims of the '008 patent cover a genus of oral liquid formulations that must contain 1 mg/mL enalapril maleate, 1.82 mg mg/mL citric acid, 0.15 mg/mL sodium citrate dihydrate, 1 mg/mL of sodium benzoate, and water, but that can contain more of the recited ingredients, and can contain any other ingredient in any other amount, as the asserted claims use the transitional phrase "comprising." However, the asserted claims also require that the claimed formulations are stable (about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period) at refrigerated conditions for at least 12 months (with dependent claims 7 and 8 requiring stability for at least 18 and 24 months, respectively).

However the common specification of the patents-in-suit provides 52 week stability data at refrigerated conditions for only two formulations falling within the scope of the asserted claims of the '008 patent—E5 and E6—and that data is incomplete, as it provides only weight percentages for two degradants, and no information on the concentration of enalapril itself at the

end of the 52 weeks. There is absolutely no data in the specification demonstrating that the claimed enalapril liquid compositions are stable according to the claimed definition (at least about 95% w/w enalapril at the end of the given storage period), for 12 months, let alone 18 or 24 months.

Moreover, formulations E5 and E6 all contained enalapril maleate, citric acid, sodium citrate anhydrous, sodium benzoate, sucralose, mixed berry flavor, and water, and no other excipients. However, as explained above, the asserted claims are not limited to these ingredients—the asserted claims cover oral liquid formulations with any other excipient imaginable, in any amount, and the POSA would know that enalapril would likely not be compatible with every other excipient, and that there were likely excipients that would accelerate degradation of enalapril, even under refrigerated conditions. The common specification provides not data, or any other assurances that the millions of oral liquids falling with the scope of the asserted claims of the '008 patent with excipients beyond the required excipients would remain stable at 12, 18, or 24 months under refrigerated conditions The POSA would simply not believe that, based on the limited data provided for formulations E5 and E6, that the named inventors were in possession of a genus of oral liquid formulations with the required amounts of enalapril maleate, citric acid, sodium citrate dihydrate, and sodium benzoate, and with additional amounts of those required ingredients, and/or with entirely different excipients in unspecified amounts, would be stable for at least 12 months at refrigerated conditions (let alone for 18 months or 24 months). *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925-28 (Fed. Cir. 2004), *In re MacLean*, 454 F.2d 758, 759 (C.C.P.A. 1972). Indeed, the POSA would also know that not every excipient would be compatible with enalapril, and that some would hasten the degradation of enalapril in a liquid formulation. The '008 patent itself admits that enalapril degrades faster in

more basic conditions (*see, e.g.*, '008 patent 13:49-38), and the POSA would know that numerous excipients that can be included in the claimed oral liquid formulations would increase the pH of those formulations and accelerate the degradation of enalapril, resulting in numerous formulations that meet the qualitative and quantitative limitations of the asserted claims but that do not meet the stability requirements of those claims.

The Mosher Declaration submitted during prosecution of at least the '008 patent further reinforces that a POSA would not have believed that the named inventors had within their possession the full scope of the claims as of the claimed priority date. The Mosher Declaration compared two new enalapril oral liquid compositions that were allegedly similar to the claimed formulations—E7 and E8, which contain qualitatively the same ingredients as formulations E5 and E6—with enalapril liquids prepared according to the Epaned Kit Patents and other references, including Nahata. '603 Appl., Feb. 3, 2017 Mosher Decl. ¶¶ 14-23. Through linear regression of available stability data for the formulations prepared according to Example 6 of the Epaned Kit Patents and the Nahata references and for the E7 and E8 formulations, Dr. Mosher demonstrated that the Example 6 and Nahata formulations—which contained additional amounts of the ingredients required in the asserted claims of the '008 patent, and/or entirely different excipients—would not have been stable at 12 months (let alone 18 or 24 months), either under refrigerated or ambient conditions. Indeed, during prosecution of the ''008 patent, Plaintiff argued that:

> [T]he prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations, much les any expectation that the combination of with [sic] enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations and pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients [disclosed in the prior art] and, through trial-and-error, determine wither each and every one of

> these components was necessary for stability or if they could be varied or eliminated.

'603 Appl., Feb. 3, 2017 Amendment at 18. The applicants repeatedly stressed the criticality of the required ingredients recited in the asserted claims of the '008 patent to the stability, and demonstrated through reliance on the Mosher Declaration that additional amounts of the required ingredients and/or additional excipients or active ingredients all together could and in fact would yield oral liquid enalapril formulations that falls within the qualitative and quantitative scope of the asserted claims of the '008 patent but not do not meet the stability requirements. The applicants failed to limit the scope of the asserted claims of the '008 patent to the E7 and E8 formulations described in the Mosher Declaration, and that failure is fatal to the asserted claims, as the common specification contains no written description for the broad scope of the asserted claims of the '008 patent. The POSA reading the common specification would simply not believe that the named inventors were in possession of the millions of enalapril oral liquid formulations falling within the qualitative and quantitative scope of the asserted claims of the '008 patent and that all of those met the required stability limitations recited in the asserted claims. To figure out what enalapril oral liquid formulations fall within the genuses recited in the asserted claims of the '008 patent, the POSA would need to engage in a trial and error process that would take at least 12 months to carry out, which is undue experimentation. Simply put, the disclosure of the '008 patent does not reasonably convey to those skilled in the art that the named inventors of the '008 patent had actually invented such a broad range of enalapril oral liquid formulations. *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1368 (Fed. Cir. 2011).

2. *The Asserted Claims of the '008 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Enablement.*

A patent is invalid if it does not "enable one of ordinary skill in the art to practice the full scope of the claimed invention." *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). "The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Nat'l Recovery Tech., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999). Factors to be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

As explained above, the asserted claims of the '008 patent cover a genus of oral liquid formulations that must contain 1 mg/mL enalapril maleate, 1.82 mg mg/mL citric acid, 0.15 mg/mL sodium citrate dihydrate, 1 mg/mL of sodium benzoate, and water, but that can contain more of the recited ingredients, and can contain any other ingredient in any other amount, as the asserted claims use the transitional phrase "comprising." However, the asserted claims also require that the claimed formulations are stable (about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period) at refrigerated conditions for at least 12 months (with dependent claims 7 and 8 requiring stability for at least 18 and 24 months, respectively).

However the common specification of the patents-in-suit provides 52 week stability data at refrigerated conditions for only two formulations falling within the scope of the asserted

claims of the '008 patent—E5 and E6—and that data is incomplete, as it provides only weight percentages for two degradants, and no information on the concentration of enalapril itself at the end of the 52 weeks. There is absolutely no data in the specification demonstrating that the claimed enalapril liquid compositions are stable according to the claimed definition (at least about 95% w/w enalapril at the end of the given storage period), for 12 months, let alone 18 or 24 months.

Moreover, formulations E5 and E6 all contained enalapril maleate, citric acid, sodium citrate anhydrous, sodium benzoate, sucralose, mixed berry flavor, and water, and no other excipients. However, as explained above, the asserted claims are not limited to these ingredients—the asserted claims cover oral liquid formulations with any other excipient imaginable, in any amount, and the POSA would know that enalapril would likely not be compatible with every other excipient, and that there were likely excipients that would accelerate degradation of enalapril, even under refrigerated conditions. The common specification provides not data, or any other assurances that the millions of oral liquids falling with the scope of the asserted claims of the '008 patent with excipients beyond the required excipients would remain stable at 12, 18, or 24 months under refrigerated conditions. The POSA would also know that not all oral liquid enalapril formulations falling within the scope of, or similar to, the claimed formulations would meet the stability requirements of the asserted claims of the '008 patent from at least the '747 patent. *See, e.g.*, '747 patent Example 6. Moreover, some of the accelerated studies reported in the '008 patent itself suggest that certain formulations falling with the scope of the asserted claims of the '008 patent would not meet the stability limitations. *See, e.g.*, '008 patent Examples A-E (study results reported for formulations at 60º C. and 4º0 C.). Further, as explained above, the Mosher Declaration, submitted during prosecution of the '603 application

demonstrates that formulations falling within the scope of, or very similar to, the claimed oral liquid formulations would not be stable according to the requirements of the asserted claims of the '008 patent for a year under refrigerated conditions, let alone for 18 or 24 months.

Indeed, the POSA would also know that not every excipient would be compatible with enalapril, and that some would hasten the degradation of enalapril in a liquid formulation. The '008 patent itself admits that enalapril degrades faster in more basic conditions (*see, e.g.*, '008 patent 13:49-38), and the POSA would know that numerous excipients that can be included in the claimed oral liquid formulations would increase the pH of those formulations and accelerate the degradation of enalapril, resulting in numerous formulations falling within the qualitative and quantitative scope of the asserted claims that do not meet the stability requirements of the asserted claims.

To figure out what oral liquid formulations fell within the scope of the asserted claims of the '008 patent, the POSA would have to go through the laborious and unduly burdensome task of preparing formulations that fall within the scope of the asserted '008 patent claims, and putting those formulations on stability testing at refrigerated conditions for a year (or longer, in the case of claims 7 and 8) and thereafter measure enalapril content and the content of any impurities or related substances. This would be undue experimentation. Moreover, the common specification provides no real guidance as to what formulations falling within the scope of the asserted claims would meet the stability requirements of those claims, and Plaintiff has argued during prosecution that the stability of the claimed formulations was dependent on the qualitative and quantitative composition of the formulation (*see, e.g.*, '603 Appl, Feb. 3, 2017 Amendment and Response at 71-13 (stressing that stability was achieved with a formulation that contained

only seven ingredients, "enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water.")).

For at least these reasons, the asserted claims of the '008 patent are invalid because they are not enabled.

3. *The Asserted Claims of the '442 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Written Description.*

As explained above, the asserted claims of the '442 patent essentially cover methods of treating heart failure and left ventricular dysfunction by administering the formulations of the asserted claims of the '008 patent. Because, as explained above, the POSA would not believe that the named inventors had actually invented the genuses of oral liquid formulations recited in the asserted claims of the '008 patent as of the priority date of the patents-in-suit, the POSA would similarly not believe that the named inventors of the '442 patent had invented the methods recited in the asserted claims of the '442 patent, which cover the administration of millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '442 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '008 patent for lack of written description, the asserted claims of the '442 patent are also invalid for lack of written description.

4. *The Asserted Claims of the '442 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Enablement.*

As explained above, the asserted claims of the '442 patent essentially cover methods of treating heart failure and left ventricular dysfunction by administering the formulations of the asserted claims of the '008 patent. Because, as explained above, it would require undue experimentation for a POSA to figure out what oral liquid formulations falling with the vast genuses of oral liquid formulations recited in the asserted claims of the '008 patent meet the stability requirements of those claims, it would similarly require undue experimentation for the

POSA to carry out the methods of the asserted claims of the '442 patent, which cover the administration of millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '442 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '008 patent for lack of enablement, the asserted claims of the '442 patent are also invalid for lack of enablement.

5. *The Asserted Claims of the '745 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Written Description.*

As explained above, asserted claims 1 and 3-10 of the '745 patent are essentially the same as asserted claims 1-10 of the '008 patent, except that asserted claims 1 and 3-10 of the '745 patent recite ranges for the required amounts of enalapril, buffer combination, and preservative (the asserted '745 patent claims also broaden enalapril to cover its pharmaceutically acceptable salts, and independent claim 1 does not include a pH limitation (although that is covered by dependent claim 6)). As also explained above, asserted claims 11 and 13-20 of the '745 patent claim the enalapril oral liquid formulations by specifying weight percentages of solids for the required enalapril, buffer combination, and preservative. Both groups of claims use the "comprising" transitional phrase between the claim preambles and the body elements, and, thus, the claimed oral liquid formulations can include more of the recited ingredients, or additional ingredients beyond the recited ingredients in any amount. Thus, the asserted claims of the '745 patent are even broader in scope than the asserted claims of the '008 patent (because the required amounts or concentrations are recited as ranges as opposed to specific amounts or concentrations).

Because, as explained above, the POSA would not believe that the named inventors had actually invented the genuses of oral liquid formulations recited in the asserted claims of the '008 patent as of the priority date of the patents-in-suit, the POSA would similarly not believe

that the named inventors of the '745 patent had invented the even broader genuses of oral liquid formulations claims of the '745 patent, which cover millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '745 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '008 patent for lack of written description, the asserted claims of the '745 patent are also invalid for lack of written description.

6. *The Asserted Claims of the '745 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Enablement.*

As explained above, the asserted claims of the '745 patent are even broader in scope than the asserted claims of the '008 patent (because the required amounts or concentrations are recited as ranges as opposed to specific amounts or concentrations). Because, as explained above, it would require undue experimentation for a POSA to figure out what oral liquid formulations falling with the vast genuses of oral liquid formulations recited in the asserted claims of the '008 patent meet the stability requirements of those claims, it would similarly require undue experimentation for the POSA to figure out what oral liquid formulations falling with the even larger genuses of oral liquid formulations recited in the asserted claims of the '745 patent, which cover millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '745 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '008 patent for lack of enablement, the asserted claims of the '745 patent are also invalid for lack of enablement.

7. *The Asserted Claims of the '987 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Written Description.*

As explained above, asserted claims 18, 20-25, and 27-30 cover methods of treating heart failure and left ventricular dysfunction by essentially administering the enalapril liquids recited in asserted claims 1 and 3-10 of the '745 patent, which, as explained above, are merely broader

versions of asserted claims 1-10 of the '008 patent. Because, as explained above, the POSA would not believe that the named inventors had actually invented the genuses of oral liquid formulations recited in the asserted claims of the '745 patent as of the priority date of the patents-in-suit, the POSA would similarly not believe that the named inventors of the '987 patent had invented the methods recited in the asserted claims of the '987 patent, which cover the administration of millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '987 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '745 patent for lack of written description, the asserted claims of the '987 patent are also invalid for lack of written description.

8. *The Asserted Claims of the '987 Patent are Invalid under 35 U.S.C. § 112(a) for Lack of Enablement.*

As explained above, asserted claims 18, 20-25, and 27-30 cover methods of treating heart failure and left ventricular dysfunction by essentially administering the enalapril liquids recited in asserted claims 1 and 3-10 of the '745 patent, which, as explained above, are merely broader versions of asserted claims 1-10 of the '008 patent. Because, as explained above, it would require undue experimentation for a POSA to figure out what oral liquid formulations falling with the vast genuses of oral liquid formulations recited in the asserted claims of the '745 patent meet the stability requirements of those claims, it would similarly require undue experimentation for the POSA to carry out the methods of the asserted claims of the '987 patent, which cover the administration of millions of oral liquid formulations that likely do not meet the stability requirements of the asserted claims of the '987 patent. For these reasons and those expressed above with respect to the invalidity of the asserted claims of the '745 patent for lack of enablement, the asserted claims of the '987 patent are also invalid for lack of enablement.

Dated: April 23, 2020

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SILVERGATE PHARMACEUTICALS, INC., *Plaintiff*, v. BIONPHARMA INC., *Defendant*.	)))))))))	C.A. No.: 18-1962-LPS C.A. No.: 19-1067-LPS

NOTICE OF SERVICE

Please take notice that copies of the following document:

BIONPHARMA'S INITIAL INVALIDITY CONTENTIONS

were served on this 23rd day of April, 2020 on counsel indicated below via electronic mail prior to 6:00 p.m. EST:

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Discovery Documents

1:18-cv-01962-LPS Silvergate Pharmaceuticals, Inc. v. Bionpharma Inc.

MEDIATION-CJB,PATENT

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District of Delaware

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